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Evaluation of liver Tissue Perfusion Characteristics with Multiphasic Dynamic CT using the Maximum Slope Model: Feasibility Study

다중 시기 전산화 단층 촬영과 최대 기울기 모형을 이용한 간 관류 영상 정보 획득: 실행 가능성 연구

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Dec 2013

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The M.S. thesis

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ABSTRACT

Purpose: To determine the feasibility of multiphasic dynamic CT including multiple arterial phases for evaluation of liver tissue perfusion characteristics using the maximum slope model in rabbits and in humans, compared with perfusion CT (PCT) as the standard of reference

Materials and Methods: In an animal study, PCT was performed in six rabbits with VX2 tumors and in five rabbits without tumors. To determine the feasibility of multiphasic dynamic CT when used to obtain perfusion parameters, two data sets were selected from the PCT data set: 1) seven-phase images including five arterial phases; and 2) five-phase images with triple arterial phases including information regarding the peak aortic and splenic enhancement. In a human study, PCT was also performed in 23 patients with chronic liver diseases. Ten of these 23 patients were classified as the validation group in order to verify the results of the animal study, and the remaining 13 patients were classified as the evaluation group. Five–phase, dynamic CT including unenhanced, triple-arterial phases and the portal phase, were selected in order to obtain perfusion parameters of liver parenchyma using a maximum slope method. Those selected CT datasets and the whole PCT data sets were analyzed using dedicated perfusion software

(VPCT body; Siemens Healthcare) for estimating the perfusion parameters. Comparison between the perfusion parameters calculated from the multiphasic dynamic CT datasets and those of PCT was made using the intraclass correlation coefficient.

Results: In the rabbit study, the perfusion parameters of both the liver parenchyma and the VX2 tumors obtained with either seven- or five-phase image data sets did not differ significantly compared with those of PCT and they showed excellent agreement with those of PCT (ICCs > 0.60, p value < 0.05). In addition, all of the perfusion parameters of patient liver parenchyma obtained by five-phase images in the 23 patients, did not differ significantly compared with those of PCT and they showed very high agreement with PCT (ICCs > 0.80, P-value < 0.01) in both the validation and the evaluation groups.

Conclusion: It was feasible to obtain perfusion parameters of the liver and tumors using multiphasic dynamic CT scans, and the perfusion parameters using the dynamic CT scans were comparable to those of perfusion CT.

Keywords:

Perfusion CT

Arterial liver perfusion

Portal venous perfusion

Hepatic perfusion index

Multiphasic dynamic CT

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INTRODUCTION

Alteration of hepatic blood flow is one of the remarkable pathophysiological changes in several important liver diseases including hepatic tumors and liver parenchymal disease such as cirrhosis [1]. With the recent technological development of MDCT and MR imaging, evaluation of hemodynamic change of the liver is possible using perfusion CT (PCT) or dynamic contrast-enhanced MRI, both of which are regarded as valuable tools for the evaluation of liver diseases including hepatic fibrosis and liver cirrhosis as well as the treatment response of liver malignancies. PCT of the liver, which was first described in 1991 [2], is one of the modalities which can acquire the liver perfusion parameters which reveal the hemodynamic changes in the liver; it has helped to expand the role of CT from a purely anatomic imaging tool to a combined morphologic-functional technique [3-7]. However, until now, PCT has been applied in clinical practice with only limited use, mainly due to concerns regarding the increased radiation dose and the poor imaging quality resulting from the use of low-tube voltage in order to decrease the radiation dose [1, 6, 8-10].

Among the various perfusion values that can be obtained using PCT, arterial liver perfusion (ALP), portal venous perfusion (PVP), and the hepatic perfusion index (HPI) are considered to be important

parameters for showing the hemodynamic features of both malignant liver tumors and liver parenchymal disease. Regarding liver parenchymal disease, such as cirrhosis, progression of cirrhosis leads to decreased portal blood flow which is compensated for by an increase in arterial flow in order to improve liver oxygenation [1]. Therefore, liver cirrhosis results in an increase of HPI, due to an increase of ALP and decrease of PVP on PCT [1, 11-13]. For malignant liver tumors, the process of neoangiogenesis which results in an increase of ALP rather than of PVP, occurs for both hepatocellular carcinoma (HCC) and metastatic hepatic tumors; there have been also several reports evaluating the changes in ALP and HPI in malignant hepatic tumors when using PCT [6, 7, 9]. There is also a recent report evaluating ALP as a prognostic factor after trans-arterial radio-embolization for hepatic metastases of colorectal cancer [14].

After the first report described by Blomley et al [12], the maximum slope model has been widely used for calculating the ALP, PVP, and HPI values from the PCT data set [1, 8, 11, 12]. Using the maximum slope model, ALP was determined by dividing the peak gradient of the liver time-attenuation curve before the peak splenic enhancement by the peak aortic enhancement, and PVP was calculated by dividing the peak gradient of the liver time-attenuation curve adjusted by scaled

splenic time enhancement after peak splenic attenuation by the peak portal trunk enhancement [8, 12]. Considering this theoretical background, there are important acquisition points, such as peak aortic enhancement, peak splenic enhancement, and peak portal enhancement timing, to obtain the ALP, PVP, and HPI value using the maximum slope model. I hypothesized that multiphasic dynamic CT scans including important time points such as arterial phases containing information regarding peak aortic or splenic enhancement and the portal venous phase providing peak portal enhancement, could be used to obtain the hepatic perfusion parameters including ALP, PVP, and HPI. Therefore, the purpose of this study is to investigate the feasibility of multiphasic dynamic CT for evaluation of liver tissue perfusion characteristics using the maximum slope model in rabbits and in humans, compared with perfusion CT (PCT) used as the standard of reference.

MATERIALS AND METHODS

Animal Model and Perfusion CT Examination

Our institutional animal care and use committee approved this animal study.

Animal model – I used 12, adult, New Zealand white rabbits, each weighing 3.0-3.5kg. A heated, circulating water blanket was used to maintain the rabbits' body temperature between 38.5°C and 39.5°C. Among the 12 adult rabbits, a VX2 carcinoma strain was maintained in six rabbits by successive transplants of tumor cells into the hind limbs of the carrier rabbits. I selected VX2 liver carcinoma for the following reasons: a) its blood supply is similar to that of human hepatocellular carcinoma (HCC); and b) it grows rapidly and to a relatively large size that is easily identified on CT images [15, 16]. After induction of anesthesia with IV ketamine hydrochloride 50 mg/Kg body weight (Ketamine, Yuhan) and 0.1 mL/Kg 2% xylazine (Rompun, Bayer Schering Pharma), a midline abdominal incision was made, and the left lobe of the rabbit's liver was exposed. A 20-gauge scalpel (Medicut, Ethicon) was used to make a tunnel approximately 0.5-1.0 cm long in the anterior subcapsular area of the left medial lobe. A 1-mm^3 portion of minced, fresh, VX2 carcinoma tissue was locally implanted through the tunnel using an ophthalmic nipper. After implantation, the incision was closed by gentle pressure using a cotton swab. This method promoted growth of a solitary, well-demarcated liver tumor in each recipient rabbit [16]. Three weeks after tumor implantation when the tumors were expected to be round and to have a 15- to 30-mm diameter,

PCT was performed.

One of the 12 rabbits without a VX2 tumor failed to inject contrast-media into the auricular vein due to extravasation during the PCT examination. Therefore, functional PCT scan was performed on the other 11 rabbits. Among the six rabbits with VX2 tumor implantation, one rabbit had one, main liver tumor with three, small, daughter nodules, and the other five rabbits had one liver tumor each. Each main tumor was included in the analysis, and the daughter nodules were excluded. The maximum diameter of all six VX tumors, as seen on axial contrast-enhanced CT scans, ranged from 1.0 to 2.8 cm (mean 1.7 ± 0.6cm).

Acquisition of perfusion CT scan - All functional PCT scanning for the rabbits was performed with an MDCT unit (Somatom Definition, Siemens Medical Solution, Erlangen, Germany). Before the CT scan, anesthesia was induced using an intramuscular injection of ketamine hydrochloride (50 mg/Kg body weight). After anesthesia, the rabbits were fixed on a board in a supine position, and an abdominal bandage was tightly applied to so as minimize motion-related artifacts. A 24-gauge scalpel (Medicut, Ethicon) was then inserted into the rabbit's auricular vein.

To determine the location of the liver and spleen, an unenhanced

CT scan was performed from the diaphragmatic dome to the pelvis using the following parameters: detector configuration, 64 x 0.6mm; rotation time, 0.5 second; pitch, 0.9; 200mAs; 120kVp; slice thickness/reconstruction interval, 1.5mm/1.5mm; and matrix, 512x512. According to the location of the liver and spleen, the scan range for PCT was selected as 11.4 cm. For functional perfusion imaging, cine CT was performed beginning three seconds prior to IV bolus injection of contrast material (iopromide, Ultravist 370, Bayer Schering Pharma) and continuing for 60 seconds. As one scanning of the whole rabbit liver took the 1.5 seconds, a total number of 40 phases was obtained for each rabbit. The contrast material was injected through the rabbit auricular vein using a power injector (Medrad, Pittsburgh, PA, USA) at a rate of 1 mL/s for four seconds [16, 17].

The PCT imaging scanning parameters were as follows: 80 kVp; effective tube current-exposure time product, 100 mAs; rotation time, 0.33 second; a cycle time, 1.5 seconds; detector configuration, 24 x 1.2 mm; and field of view, 12 cm^2. The CT scans were reconstructed with the following parameters: slice thickness, 1 mm; no gap; matrix size, 512 x 512; scan range, 11.4cm; and total image number, 4560.

Patient Selection and Perfusion CT Examination

In the present study, I retrospectively analyzed a prospectively collected perfusion CT data of a prospective clinical trial. The phase IV clinical trial was registered at http://www.clinicaltrials.gov (study number: ISO44-013) for pretherapeutical CT perfusion assessment of hepatocellular carcinoma using Xenetix.

From July 2012 to July 2013, 26 consecutive patients underwent perfusion CT for pretherapeutic assessment of hepatocellar carcinoma. Among these patients, three were excluded from the PCT analysis for the following reasons: greater than 10-cm HCC involving the entire right lobe of the liver (n=2); time-enhancement curve showing two–peak aortic enhancement timing following contrast injection (n=1). Finally, 23 patients (M:F=20:3, mean age; 56.8 ± 12.0) were included in this study, and we evaluated this PCT data retrospectively. The Institutional Review Board of our medical institution approved this retrospective study, and written, informed consent had been obtained from all included patients.

Acquisition of perfusion CT scan - Initially, a non-contrast scan was obtained through the entire liver. After that, 50ml of nonionic contrast material (370 mg I/ml, Xenetix 370; Guerbet) was injected at a flow rate of 5ml/sec through an 18-gauge catheter which had been placed into the antecubital vein. 50 ml of normal saline flush injected at

the same rate then followed. Scans started five seconds after injection of the contrast material, and which ensured 40 seconds of scans with contrast and the first five seconds without contrast. The scan duration was 21 stacks with a cycle time of 1.5 seconds. After the 21 stacks of continuous scanning, five additional scans with a 1.5-second scan duration each and a 1.5-second inter-scan delay, were obtained. The scan coverage was selected as 10 cm. The scanning parameters for perfusion CT were as follows: detector collimation of 64 x 0.625mm; and a gantry rotation time of 0.5 second. The effective tube current was 200mAs at 80kVp for slim patients (BMI<21), 100mAs at 100kVp for normal-sized patients (BMI;21-28), and 150mAs at 100kVp for patients whose BMI was greater than 28. All images were reconstructed with 2-mm thickness at 2-mm increments. In term of the radiation dose for the triple arterial phase acquisition protocol used in this study, the mean effective radiation dose ranged from 14.0 to 22.0 mSv (mean: 16.7 mSv).

Analysis of the Perfusion Parameters

The reconstructed image data were transferred to an imaging workstation (Leonardo; Siemens Medical Solutions) for analysis using perfusion CT software (VPCT body, Siemens Medical Solutions,

Erlangen, Germany) based on the maximum slope model. Before the perfusion analysis processes, motion correction was applied for both each rabbit and each patient. As the liver moves in a complicated fashion during breathing, non-rigid warping techniques are required for registration [18], and the VPCT software program used in this study has a dedicated, high-performance algorithm. Pixels within the range of -50 to 150HU values were selected to exclude bone, air, and contrast-material densities. The aorta was chosen as the input artery and the portal vein as the venous input. Spleen parenchyma was also selected to determine timing of peak splenic enhancement, which is very important for dividing arterial and portal blood flow to the liver according to the maximum slope model. I drew regions of interest (ROIs) on the aorta, portal vein, and spleen parenchyma in a representative, transverse plane (Figure 1a), after which we obtained the time-enhancement curves (Figure 1b).

To quantify the perfusion parameters, I placed ROIs on both the representative liver parenchyma (Figure 1c) and the VX2 carcinomas (Figure 1d). For the analysis of VX2 carcinoma, the ROIs were drawn by outlining the viable tumor portion, as depicted by strong enhancement at the tumor periphery. The parametric perfusion maps of the arterial liver perfusion (ALP) (ml $100ml^{-1}$ min^{-1}), portal venous

liver perfusion (PVP) (ml $100ml^{-1}$ min^{-1}), and the hepatic perfusion index (HPI, %) which is the ratio of the hepatic arterial perfusion to the total perfusion, were generated using a high-spatial-resolution, pixel-by-pixel calculation technique, and the values of the ROIs I had placed were automatically calculated (Figure 1c and Figure 1d).

Determining the Number of Phases Required for Calculating Perfusion Parameters Using Multiphasic Dynamic CT in an Animal Model

On the basis of the time-enhancement curves, I extracted the required phases containing crucial information such as the peak aortic or splenic enhancement, from the PCT data set used for calculating the perfusion parameters including ALP, PVP, and HPI. According to the time-enhancement curve, the following contrast enhancement information was obtained: the proximal abdominal aorta had reached 100 HU approximately three seconds after beginning the contrast injection; the peak aortic enhancement achieved approximately six seconds after the proximal abdominal aorta had reached 100 HU; and the peak spleen parenchymal enhancement was seen approximately six seconds after the peak aortic enhancement. To select the phases required in order to obtain ALP, PVP, and HPI, I simulated the bolus-

tracking method which is currently used in many medical institutions for multiphasic, contrast-enhanced CT. As the aorta reached its peak enhancement six second after triggering, i.e. the proximal abdominal aorta had reached 100 HU, I considered this arterial phase as the reference arterial phase. To determine the minimum number of phases of multiphasic dynamic CT scanning required to calculate ALP, PVP, and HPI, I used two different methods. First, I selected seven phases, including unenhanced, five arterial and the portal-venous phase. The five arterial phases consisted of two more phases earlier and later than the reference arterial phase and with a three-second interval. Therefore, five arterial phases included the phase obtained after just 100 HU of the abdominal aortic enhancement timing, and three, six, 9, and 12 seconds after triggering. The portal venous phase was defined as 25 seconds after enhancement in the aorta reached 100 HU, as it then showed maximum hepatic parenchymal enhancement [16]. Second, I selected five phases, including unenhanced, triple arterial, and the portal-venous phase. Triple arterial phases consisted of an additional phase earlier and later than the reference arterial phase. We used a six-second interval rather than a three-second interval in our selection of the triple arterial phases as peak splenic enhancement timing was obtained six seconds after peak aortic enhancement. Therefore, selected triple arterial phases

included the phase obtained after just 100 HU of abdominal aortic enhancement timing, and six and 12 seconds after triggering. I hypothesized that seven-phase image data sets were closer to the results of PCT when compared with five-phase images data sets because more contrast-enhancement information was included in seven-phase images.

The selected phase CT images were transferred to a workstation (Leonardo; Siemens Medical Solutions) equipped with commercially available software (VPCT body, Siemens Medical Solutions). After motion correction using non-rigid warping techniques implemented using VPCT body software, the ROIs were placed on the aorta, portal vein, and spleen parenchyma in a representative transverse plane, and the time-enhancement curves were obtained in a similar manner to that used for functional PCT analysis (Figure 2). To obtain the perfusion parameters, I placed ROIs on the representative liver parenchyma and the viable portion of the VX2 carcinomas in a similar manner to that used in functional PCT analysis. The parametric perfusion maps of ALP, PVP, and HPI using a high-spatial-resolution, pixel-by-pixel calculation technique and the values of the ROIs placed were automatically calculated.

Analysis of the Perfusion Parameters Using Multiphasic Dynamic

CT in Patient Liver

I randomly categorized 23 patients into two groups: the validation group (n=10) and the evaluation group (n=13). Use of the five–phase, dynamic CT data set for obtaining ALP, PVP, and HPI were verified in the validation group patients as the animal model showed that the five-phase image data set could provide the ALP, PVP, and HPI values. According to the time-enhancement curve obtained in the validation group, the following contrast-enhancement information was obtained: the peak aortic enhancement achieved approximately nine seconds after the proximal abdominal aorta had reached 100 HU, and the peak spleen enhancement was seen approximately nine seconds following peak aortic enhancement, i.e. 18 seconds after triggering. Peak portal vein enhancement was seen approximately nine seconds following peak splenic enhancement, i.e. 27 seconds after triggering

For obtaining perfusion parameters, including ALP, PVP, and HPI, we used the five-phase dynamic CT data set including unenhanced, triple arterial, and the portal venous phase. As peak splenic enhancement was achieved approximately nine seconds after peak aortic enhancement, we used a nine-second interval for the selection of triple arterial-phase images. Therefore, selected triple arterial phases included the phase obtained with just 100 HU of abdominal aortic

enhancement timing, nine and 18 seconds after triggering. The portal venous phase was selected as 50 seconds after enhancement when the aorta reached 100 HU. The selected phase CT images were then transferred to a workstation (Leonardo; Siemens Medical Solutions), and perfusion analysis processes were performed using commercially available software (VPCT body, Siemens Medical Solutions) in a similar manner to that of the rabbit analysis described above. We also evaluated the six-phase dynamic CT data set including the five-phase dynamic CT data set and the additional phase containing peak portal vein enhancement timing in order to determine the significance of the peak portal vein enhancement timing for obtaining ALP, PVP, and HPI values.

In the evaluation group patients, the five–phase, dynamic CT data set including unenhanced, triple arterial phase images (the phase obtained with just 100 HU of abdominal aortic enhancement timing, nine and 18 seconds after triggering) and the portal venous phase were transferred to a workstation (Leonardo; Siemens Medical Solutions) and were then analyzed with perfusion software to obtain the ALP, PVP, and HPI values.

Statistical Analysis

Perfusion parameters including ALP, PVP, and HPI determined by PCT and by selected phases of the dynamic CT scan were compared using repeated measures one way analysis of variance (ANOVA). Two-tailed $p < 0.05$ was considered as indicating a significant difference. When the significant differences were observed, the post hoc, pair-wise student t-test with Bonferroni correction was used to determine where the significant difference existed.

To assess the agreement and correlation between the parameters obtained by PCT and the parameters obtained by each of the selected phases of dynamic CT, the intraclass correlation coefficient (ICC) and its two-tailed p-value were also obtained. We considered an ICC value of more than 0.81 to represent almost perfect agreement and values of 0.61–0.80, 0.41–0.60, and 0.21-0.40 to represent substantial, moderate, and fair agreement, respectively. A value less than 0.20 was considered to represent slight agreement. All statistical analysis was performed using SPSS version 21 (SPSS, Chicago, IL, USA).

RESULTS

Perfusion Parameters Obtained Using PCT and Multiphasic Dynamic CT in Rabbits

Perfusion parameters including ALP, PVP, and HPI determined by PCT and by each selected phase dynamic CT data set are summarized in Table 1. For PCT, the mean ALP, PVP, and HPI of the liver parenchyma were 14.2 ml $100ml^{-1}$ min^{-1}, 49.4 ml $100ml^{-1}$ min^{-1}, and 23.0%, respectively. All of the perfusion parameters obtained by the seven-phase images data set and by the five phases did not differ significantly from that of the functional PCT regarding both the liver parenchyma and the viable portion of VX2 carcinoma.

Intraclass Correlation Coefficients of Perfusion Parameters in a Rabbit

The intraclass correlation coefficients between the perfusion parameters of PCT and the perfusion parameters obtained from each of the selected phases of the dynamic CT are summarized in Table 2. In terms of liver parenchyma, the seven-phase images data set and the five phases showed statistically significant ICC values and revealed almost perfect agreement with PCT regarding all of the perfusion parameters. Regarding the viable portion of VX2 carcinoma, the seven-phase images data set and the five phases showed substantial to almost perfect agreement with PCT regarding ALP, PVP, and HPI. Despite the fact that some of the ICC values were not statistically significant, e.g. ICC

of PVP (p-value, 0.098) and HPI (p-value, 0.109) for the seven-phase images data set, ICC of ALP (p-value, 0.056) for the five-phase images data set, the ICC values showed a tendency toward correlation and agreement.

Perfusion Parameters Obtained in Patient Liver

Perfusion parameters obtained using the PCT and multiphasic dynamic CT data set, both five- and six-phase, and the ICC values between the perfusion parameters with its P-values in the validation group, are summarized in Tables 3. All of the perfusion parameters obtained using the five- and-six phase dynamic CT data set did not differ significantly from that of the PCT. Regarding ICCs between the PCT and the multiphasic dynamic CT data set, substantial to almost perfect agreement was seen for all perfusion parameters and these ICCs were also statistically significant in validation groups of patients. Therefore, in the evaluation group, only the five-phase dynamic CT data set and the full PCT data set were compared, and the results are summarized in Table 4. All perfusion parameters obtained from both the five-phase dynamic CT data set and the PCT did not differ significantly, and almost perfect agreement was seen between the five-phase dynamic CT and the PCT data set in the evaluation group.

DISCUSSION

In this study, multiphasic dynamic CT scans, including important time points, could provide ALP, PVP, and HPI values with the use of the maximum slope model. ALP, PVP, and HPI values can be obtained from both the seven- and the five-phase dynamic CT data sets in rabbit liver, and these values did not differ significantly from those of PCT. Indeed, substantial to almost perfect agreements with PCT were seen for both the seven- and the five-phase images data set.

For assessing liver parenchyma, none of the perfusion parameters obtained by either the seven-phase dynamic CT data set or five-phase images differed significantly from that of functional PCT. Furthermore, in terms of the correlation and agreement assessed by ICCs, all of the perfusion parameters obtained by the seven-phase and five-phase dynamic CT data sets significantly agreed with and were correlated with that of functional PCT, and the ICC values showed almost perfect agreement. In terms of assessing the viable portion of VA2 carcinoma, there was no significant difference between the PCT perfusion parameters and those of the seven- or five-phase images data sets. For agreement of perfusion parameters between the PCT and multi-arterial phase data sets, the ICC values of the seven- and five-phase images

data sets showed substantial to almost perfect agreement with PCT regarding ALP, PVP, and HPI. However, in contrast to the liver parenchyma, some ICCs values were not statistically significant, and the ICC values tended to be less than those for the liver parenchyma. This different finding from that of the normal liver parenchyma could be explained by several factors. First, the number of examined tumors was much smaller than the number of examined liver parenchyma. As six rabbits had VX2 carcinoma in each liver, only six VX2 carcinoma nodules could be examined. The small number of examined VX2 carcinomas might limit the statistical strength of the analysis for the assessment of ICCs. Second, the VX2 carcinomas were more heterogeneous in nature than normal liver parenchyma. Therefore, exact assessment of the perfusion parameters in VX2 carcinoma was somewhat more difficult than evaluation of the perfusion parameters in normal liver parenchyma.

In contrast to my expectation, I could not find any significant difference between the rabbit perfusion parameters obtained from seven- and five-phase dynamic CT data sets regarding any perfusion parameters. Therefore, I thought that inclusion of arterial phases which contained crucial information such as the peak aortic or splenic enhancement timing for estimating the perfusion parameters, was more

important than the total number of arterial phases used. I also found that the peak portal vein enhancement timing did not have significant influence on the estimation of the perfusion parameters, including the ALP, PVP, and HPI in the validation group of patients. This result might be explained as follows: in contrast to the arterial enhancement, portal vein enhancement was sustained for a relatively long time after peak enhancement reached, and the decrease in the enhancement degree in the portal vein was much slower than that of the artery. Therefore, the portal vein enhancement degree might not differ significantly between the portal-venous phase and the phase of peak portal vein enhancement, i.e. somewhat earlier than the portal-venous phase in this study, and thus causing a significant difference in the calculating perfusion parameters. Considering these results, it was feasible that obtaining the ALP, PVP, and HPI values using the five-phase dynamic CT data set, including the triple arterial phase containing the crucial information regarding the peak aortic or splenic enhancement and the obtained values, did not differ significantly from those obtained from the full PCT data set. For the application of the five–phase, dynamic CT data set in order to obtain the ALP, PVP, and HPI in patient liver, detailed contrast-enhancement characteristics of human beings, including information regarding how long it took to reach the peak

aortic and splenic enhancement after triggering, i.e. enhancement in the proximal abdominal aorta reached 100 HU, should be defined. In our preliminary results, peak aortic enhancement was seen approximately nine seconds after enhancement in the proximal abdominal aorta reached 100HU, and peak splenic enhancement was achieved approximately 18 seconds after triggering in the validation group. Given that peak splenic enhancement was usually seen in the late-arterial phase and previously established late arterial-phase images could be obtained 17 to 18 seconds after triggering, our patient results in the validation group corroborate these findings. I also analyzed the evaluation group and obtained the ALP, PVP, and HPI values using the five–phase, dynamic CT data set with the information regarding contrast kinetics regarding peak aortic and splenic enhancement from the validation group. In the evaluation group of patients, the values of the ALP, PVP, and HPI obtained from the five-phase dynamic CT data set, did not differ significantly from that of the full PCT data set and also showed almost perfect agreement with the PCT results. Considering these results, it was feasible to obtain the ALP, PVP, and HPI values from the five–phase, dynamic CT data set, including the triple-arterial phases containing crucial enhancement information. However, this study results should be verified in a large series study.

Regarding the exposed radiation dose, the five–phase, dynamic CT data set clearly required less radiation than the full PCT data set. As the PCT protocol used in this study included a total number of 40 phase images for rabbits and included 36 phases for patients, theoretically, approximately one-eighth of the radiation dose was needed for the five-phase dynamic CT data set compared with the full PCT data set. Therefore, this study result suggests the possibility of extending the clinical application of perfusion imaging and decreasing the radiation dose for obtaining the perfusion parameters. To reduce the radiation dose in five-phase dynamic CT acquisition for estimating the ALP, PVP, and HPI, an iterative reconstruction algorithm can also be used [19, 20]. With the technical development of MDCT, such as wider detector coverage, five–phase, dynamic CT scanning can also cover the entire liver, thus making simultaneous assessment of the morphologic and functional evaluation possible. All of these technical developments might expand the role of CT to functional imaging. Information regarding hemodynamic changes in malignant tumor or liver parenchyma may provide crucial information for clinical practice. For example, perfusion parameters can predict the tumor response in the treatment of pancreatic or rectal cancer [21, 22]. Recently, Morsbach et al. reported that the ALP of metastatic colon cancer in liver could be

used as a prognostic factor after trans-arterial radio-embolization [14]. Perfusion imaging can also be used to predict tumor response to antiangiogenic drug therapy [23]. This study results might suggest the possibility of clinical application of perfusion imaging as it decreases the radiation dose and increases scanning coverage.

This study had several limitations which should be mentioned. First, the number of rabbits and patients included in this study was relatively small, and the animal sample was uniform i.e. clonal VX2 carcinomas in otherwise healthy, similar-sized rabbits without any hepatic or cardiovascular diseases and which could alter the hepatic hemodynamic. Therefore, the study design might be optimistic rather than useful in actual clinical practice. Second, I extracted needed phases for obtaining the ALP, PVP, and HPI from the PCT data set, and the rescanning according to the multiphasic dynamic CT acquisition protocol defined by our study result was not performed and might also have resulted in optimistic study results. The duration, volume, and concentration of contrast injection between the multiphasic dynamic liver CT and PCT can differ and this difference can alter the perfusion parameter analysis. Third, the calculated perfusion parameters in the maximum slope model also depend on the bolus volume, rate of injection, and cardiac output, and we did not assess the influence of

these parameters on the calculated ALP, PVP, and HPI. Noise level in the images also affects the calculated perfusion parameters and must be minimized in order to achieve the optimal outcome. We also did not assess the influence of the noise level on the estimated ALP, PVP, and HPI values. Fourth, VX2 carcinoma is a metastatic hepatic tumor model with prominent neoangiogenesis, and which differs from HCC in that an HCC shows capillary formation in sinusoidal endothelium with neoplastic transformation. Thus, the application of our study results may be somewhat limited to the evaluation of liver metastasis.

In conclusion, obtaining perfusion parameters using a multiphasic dynamic CT scan data set was feasible, and five phases including crucial contrast enhancement information might be sufficient for calculating the ALP, PVP and HPI values. In addition, the perfusion parameters of the liver and the VX2 tumors using the dynamic CT scans were comparable with those of the PCT.

TABLES

Table 1. Perfusion parameters determined by PCT as well as by both the seven- and five-phase dynamic CT data sets

		PCT	Seven phases	Five phases	p-value*
Parenchyma (n=11)	ALP (mean ± SD)	14.2 ± 3.6	15.4 ± 3.7	16.0 ± 4.4	0.132
	PVP (mean ± SD)	49.4 ± 12.2	51.7 ± 14.5	53.9 ± 16.1	0.376
	HPI (mean ± SD)	23.0 ± 2.1	23.6 ± 2.7	23.3 ± 2.2	0.235
Tumor (n=6)	ALP (mean ± SD)	29.5 ± 3.8	29.7 ± 6.0	26.5 ± 4.4	0.867
	PVP (mean ± SD)	4.6 ± 2.1	5.9 ± 1.8	4.4 ± 1.9	0.149
	HPI (mean ± SD)	87.0 ± 2.6	86.6 ± 3.5	87.8 ± 4.3	0.753

*, the p-value was determined by repeated measures one-way analysis of variance.
ALP, arterial liver perfusion (ml $100ml^{-1}$ min^{-1})
PVP, portal venous liver perfusion (ml $100ml^{-1}$ min^{-1})
HPI, hepatic perfusion index (%)
CT, computed tomography
SD, standard deviation

Table 2. Intraclass correlation coefficients between the perfusion parameters of PCT and those of both the seven- and five-phase dynamic CT data set

		PCT vs. seven phases	PCT vs. five phases
Parenchyma (n=11)	ALP [ICCs (p-value)]	***0.855 (0.002)***	***0.856 (0.001)***
	PVP [ICCs (p-value)]	***0.894 (0.001)***	***0.911 (< 0.001)***
	HPI [ICCs (p-value)]	***0.855 (0.002)***	***0.854 (0.003)***
Tumor (n=6)	ALP [ICCs (p-value)]	***0.909 (0.014)***	0.701 (0.056)
	PVP [ICCs (p-value)]	0.654 (0.098)	***0.723 (0.024)***
	HPI [ICCs (p-value)]	0.729 (0.109)	***0.670 (0.044)***

PCT, functional perfusion computed tomography
ICC, intraclass correlation coefficient
ALP, arterial liver perfusion
PVP, portal venous liver perfusion
HPI, hepatic perfusion index

Table 3. Perfusion parameters determined by PCT and the multiphasic dynamic CT data set in the validation group of patients

	PCT	Five phase	Six phase	p-value*	ICC (p-value) PCT vs 5P	ICC (p-value) PCT vs 6P
ALP	9.90 ± 2.27	10.49 ± 2.40	11.27 ± 3.24	0.127	0.848 (<0.001)	0.691 (0.009)
PVP	24.67 ± 6.78	26.40 ± 6.73	25.26 ± 5.41	0.368	0.910 (<0.001)	0.761 (0.003)
HPI	29.31 ± 8.56	29.40 ± 8.90	31.44 ± 9.87	0.131	0.969 (<0.001)	0.938 (<0.001)

*, p-value was determined by repeated measures one-way analysis of variance.
PCT, functional perfusion computed tomography
ICC, intraclass correlation coefficient
ALP, arterial liver perfusion (ml $100ml^{-1}$ min^{-1})
PVP, portal venous liver perfusion (ml $100ml^{-1}$ min^{-1})
HPI, hepatic perfusion index (%)
PCT, functional perfusion computed tomography

Table 4. Perfusion parameters determined by PCT and by the five-phase dynamic CT data set in the patient evaluation group

	PCT	Five phases	P-value*	ICC (p-value)
ALP	9.77 ± 1.83	10.18 ± 1.84	0.227	***0.806 (<0.001)***
PVP	27.51 ± 5.02	29.10 ± 4.40	0.139	***0.772 (<0.001)***
HPI	26.40 ± 4.38	26.09 ± 3.97	0.362	***0.959 (<0.001)***

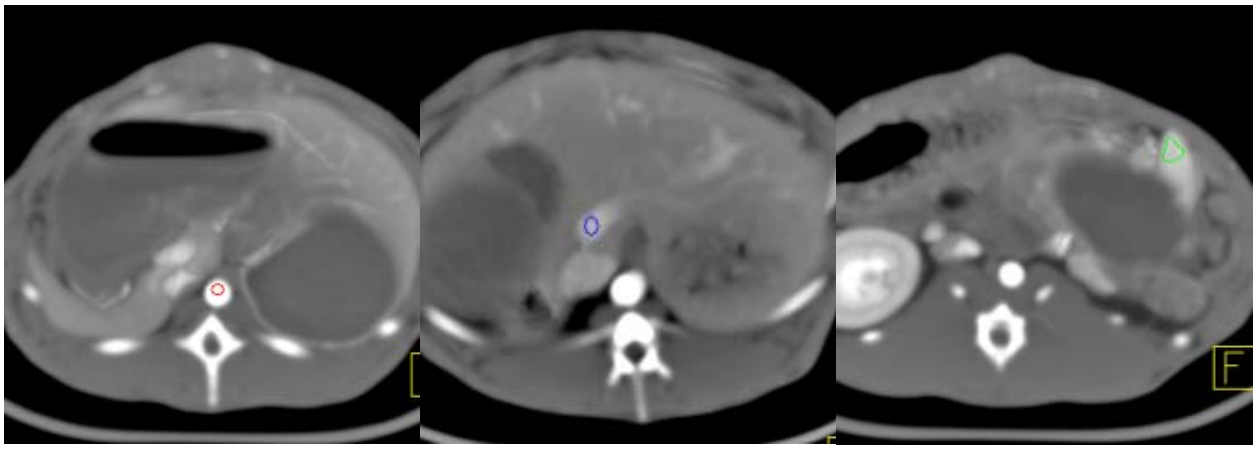
*, p-value was determined by paired t-test
PCT, functional perfusion computed tomography
ICC, intraclass correlation coefficient
ALP, arterial liver perfusion (ml $100ml^{-1}$ min^{-1})
PVP, portal venous liver perfusion (ml $100ml^{-1}$ min^{-1})
HPI, hepatic perfusion index (%)
PCT, functional perfusion computed tomography

Figures

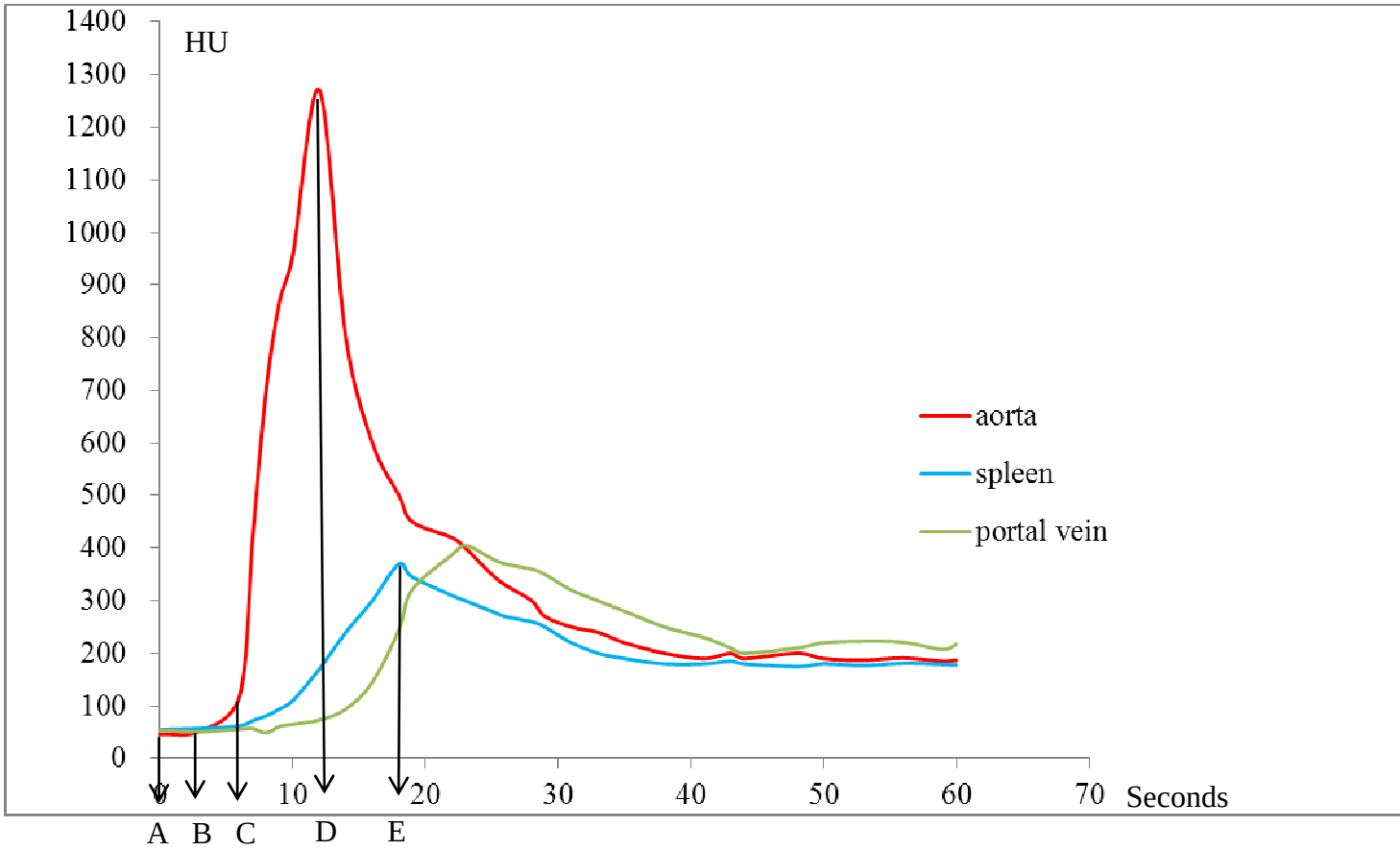
Figure 1. PCT analysis.

*PCT: perfusion CT

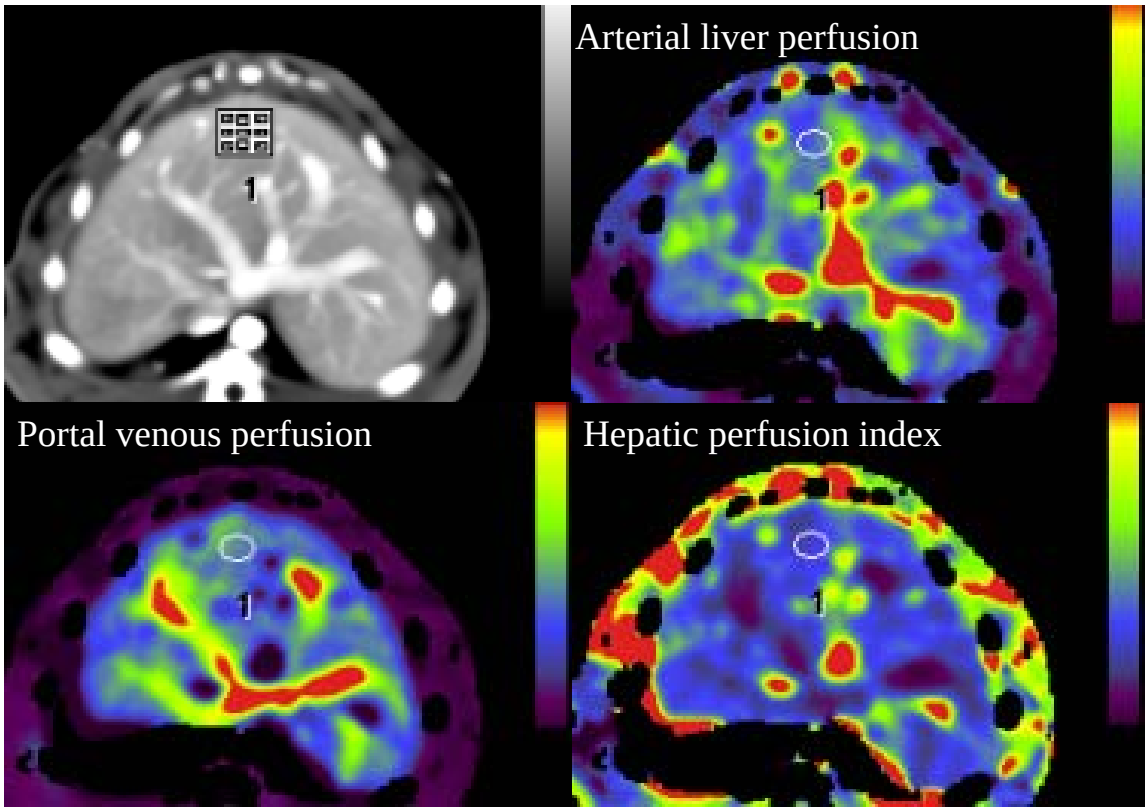
(a) Contrast enhanced transverse CT images of rabbit shows placement of regions of interest (ROIs); left (aorta), middle (portal vein), and right (spleen). Aorta is input artery, and portal vein is venous input.



(b) Time-enhancement curves of the selective ROIs obtained from functional perfusion CT data. A represents scan start and B, C, D and E represent start of contrast injection, proximal abdominal aorta reached 100 HU (triggering point in bolus tracking method), peak aortic enhancement and peak spleen parenchyma enhancement, respectively.



(c) The ROIs was placed on rabbit liver parenchyma, and the parametric perfusion maps with a high-spatial-resolution pixel-by-pixel calculation technique, and the values of the ROIs placed were automatically calculated.



(d) The ROIs was placed on viable portion of VX2 carcinoma, and the parametric perfusion map was made with similar manner used for liver parenchyma.

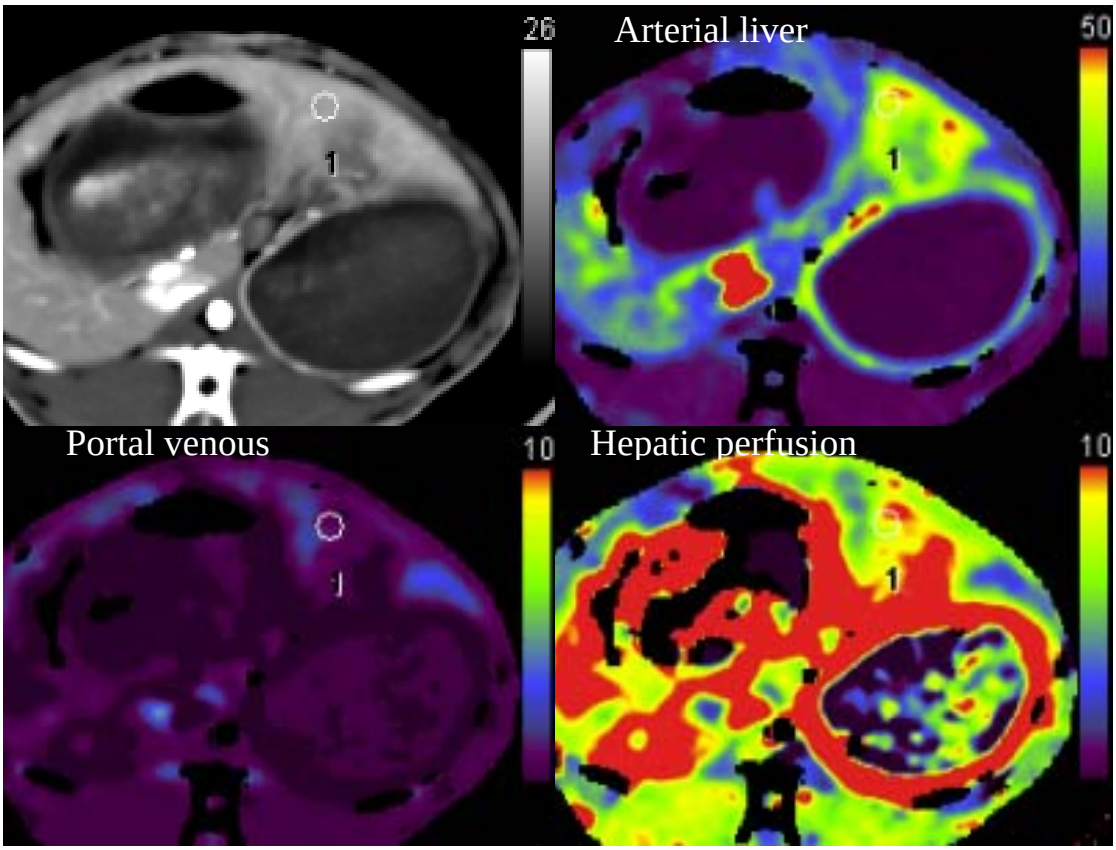
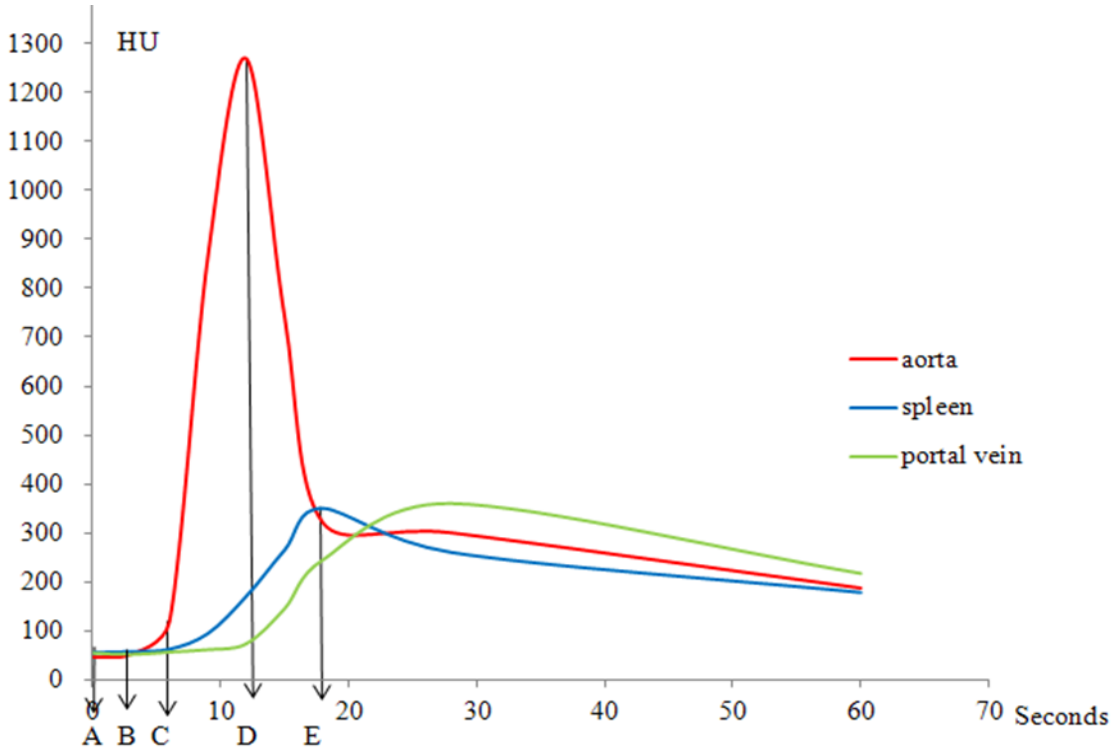
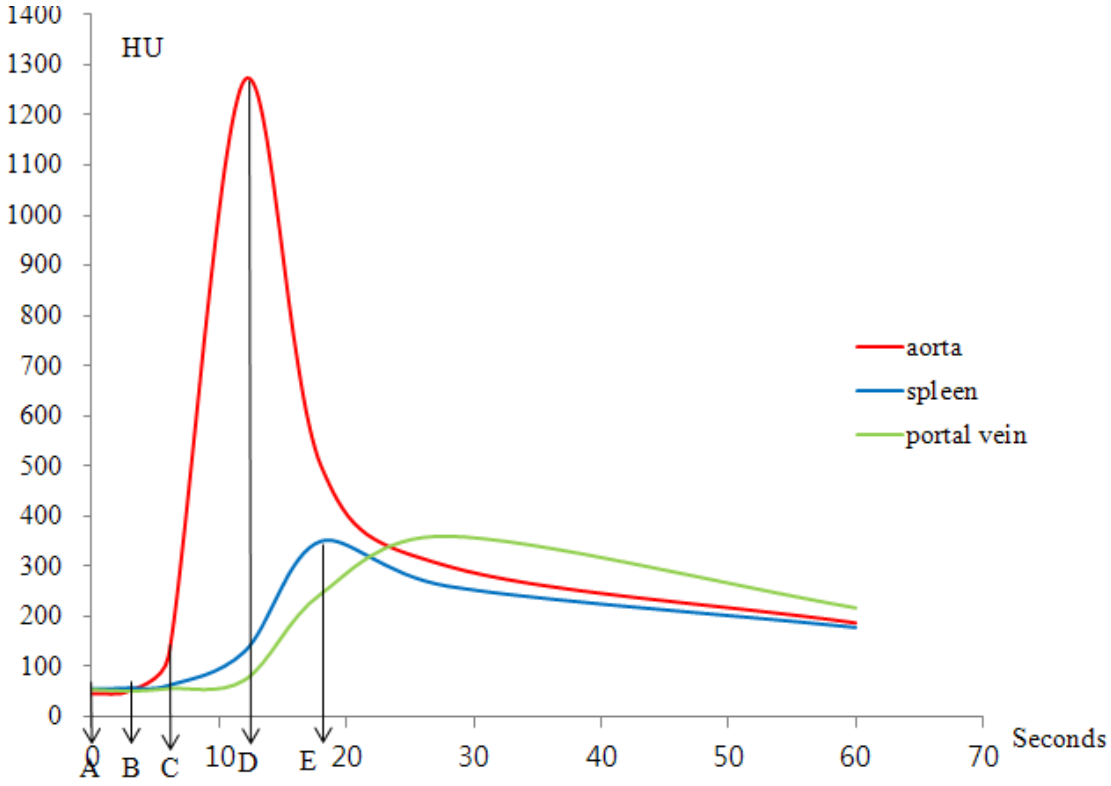


Figure 2. Time-enhancement curves obtained by seven and five phase dynamic CT data set;

(a) seven phase dynamic CT data set,



(b) five phase dynamic CT data set. A represents scan start and B, C, D and E represent start of contrast injection, proximal abdominal aorta reached 100 HU (triggering point in bolus tracking method), peak aortic enhancement and peak spleen parenchyma enhancement, respectively.



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국문 초록

목적: 다중시기 전산화 단층 촬영과 최대 기울기 모형을 이용하여 간 관류 정보 획득의 실행 가능성을 토끼를 이용한 동물 모델과 환자군 에서 관류 전산화 단층 촬영의 결과를 표준으로 이용하여 평가한다.

방법: 관류 전산화 단층 촬영을 11마리의 토끼에서 시행하였으며 이중 6마리의 토끼는 VX2 종양을 가지고 있었다. 다중시기 전산화 단층 촬영을 이용하여 관류 정보 획득 가능성을 평가하기 위하여 토끼를 이용한 동물 모델에서 두 가지 다른 영상 데이터 집합을 관류 전산화 단층 촬영 데이터 집합에서 선택하였다: 첫 번째, 다섯 시기 동맥기 영상을 포함한 일곱 시기 영상 데이터 집합; 두 번째, 최대 대동맥 조영 시기와 최대 비장 조영 시기의 정보를 가지고 있는 삼중 동맥기 영상을 포함한 다섯 시기 영상 데이터 집합.

환자군 연구에서는 만성 간질환을 가진 23명의 환자에서 관류 전산화 단층 촬영을 시행하였다. 이중 10명의 환자는 토끼를 이용한 동물 모델에서의 결과를 확인하기 위한 입증군으로, 13명의 환자는 평가군으로 나누었다. 삼중 동맥기 영상, 비조영 영상, 간문맥기 영상을 포함한 다섯 시기 영상 데이터 집합이 최대 기울기 모형을 이용한 관류 정보 획득에 이용되었다. 선택된 각각의 다중 시기 전산화 단층 촬영 영상 데이터의 집합과 관류 전산화 단층 촬영의 데이터 집합은 VPCT body라는 관류 영상 소프트웨어를 이용하여 분석하였다. 각 데이터 집합에서 얻어진 관류 정보 값들 사이의 비교와 일치도를 평가하기 위하여 반복 측정 분산 분석과 급내 상관 계수를 이용하였다.

결과: 토끼를 이용한 동물 모델에서 간 실질과 VX2 종양에 대해 얻어진 관류 정보 값들은 관류 전산화 단층 촬영

데이터를 이용하거나 일곱 시기 혹은 다섯 시기 전산화 단층 촬영 데이터 집합을 이용하였을 때 모두 유의하게 다르지 않았으며, 0.6 이상의 급내 상관 계수가 얻어져 상당한 정도의 일치도를 보였다. 또한, 환자군 연구에서 간 실질에 대해 얻어진 관류 정보의 값들은 관류 전산화 단층 촬영 데이터를 이용하거나 다섯 시기 전산화 단층 촬영 데이터 집합을 이용하였을 때 모두 유의하게 다르지 않았으며, 급내 상관 계수 0.8 이상의 높은 일치도를 보였다.

결론: 다중 시기 전산화 단층 촬영과 최대 기울기 모형을 이용하여 간 관류 정보 값의 획득은 가능하며, 이렇게 다중 시기 전산화 단층 촬영을 이용하여 얻어진 관류 정보 값은 관류 전산화 단층 촬영을 이용하여 얻은 관류 정보 값과 유사하며 높은 일치도를 보인다.